sequence GCCTCTGGGGAG (SEQ ID NO:1) in proximity to the Sp-1 binding site, whereby expression of the heterologous protein is regulated in a tissue specific manner.

REMARKS

This submission is in response to the Official Action dated July 16, 2002. Claims 28-30, 33 and 34 have been amended. New claims 38 and 39 have been added. Unelected claims 1, 2 and 22-27 have been cancelled without prejudice or disclaimer. Claims 28-39 are currently pending.

Claims 28 and 33 have been amended to fully write out an abbreviation in the claims ("β_3-adrenergic receptor (β_3-AR)" for "β_3-AR" the first time it appears in the claim). Support for this amendment is found throughout the specification and in particular on p. 1 line 13 of the specification. Claims 28 and 33 have also been amended to more particularly recite the subject matter of the present invention. In particular, they have been amended to recite two β_3-adrenergic receptor *trans*-activating factors: the Sp1 and B segment-binding β_3-adrenergic receptor *trans*-activating factors. Support for these amendments is found on p. 9 line 16- 26, p. 48 lines 21-p.49 line 12, and p. 55 line 12-22.

Claim 29 has been amended to incorporate the limitations of original claim 28 and thus, no new matter has been added by way of this amendment. Claim 30 has been amended to depend upon claim 28 and thus, no new matter has

been added by way of this amendment.

Claim 34 has been amended to be written in independent form and incorporate the limitations of the claim from which it depended, claim 33. Thus, no new matter has been added by way of this amendment.

New claims 38 and 39 have been added. New claim 38, in part, corresponds to original claim 29. New claim 39, in part, corresponds to original claim 34. These new claims are also supported throughout the specification. In particular, new claims 38 and 39 are supported at page 29 line 5- page 30 line 7 (use of reporter gene to screen for factors that increase or decrease β_3-AR activity); page 7, line 29 to page 8, line 1; page 10, line 22; and page 11, lines 20-21 (about a 7 kb genomic DNA located upstream of a β_3-AR transcription start site); page 8, lines 1-2 and page 11, lines 25-26 (a deletion construct of a 7 kb genomic DNA located upstream of a β_3-AR transcription start site); page 14, lines 15-17 (heterologous coding sequence); page 11, line 27 (promoter); page 13, lines 8-10 (use of the regulatory elements in a recombinant expression vector); and page 5, line 1 and page 8, lines 18-20 (regulated, tissue-specific expression). Claim 1 is further supported at page 8, line 13 and page 10, line 8 (*trans*-activator binding site); page 5, line 4 and page 11, lines 14-15 (proximity); claim 3 as filed (nucleotide sequence that binds an Sp-1 transcription factor protein); and page 11, line 7 (alternative arrangement of the *trans*-activator binding site and the Sp-1 binding site as set forth in part (c) of claim 1).

No new matter has been added by these amendments. Reconsideration of the above identified application, in view of the above amendments and the following remarks, is respectfully requested.

REJECTIONS UNDER 35 USC § 112, FIRST PARAGRAPH

The Examiner has rejected claims 28, 31-33 and 35-37 as allegedly failing to fulfill the written description requirement. Specifically, the Examiner contends that one skill in the art would not be able to envision a sufficient number of *trans*-activating factors involved in expression of β_3-AR to describe the genus of such factors embraced by the claims.

Claims 28 and 33 (claims 31 and 32 depend from claim 28, and claims 35-37 depend from claim 33) have been amended to recite specific β_3-AR *trans*-activating factors, specifically the Sp1 or B segment-binding β_3-adrenergic receptor *trans*-activating factors. The Examiner has expressly stated that these factors are described in the application (see p. 3 lines 5-6 of the July 16, 2002 Office Action). Thus, it is believed that these rejections have been overcome and Applicants respectfully request that they are withdrawn.

REJECTIONS UNDER 35 USC §112, SECOND PARAGRAPH

The Examiner has rejected claim 31 as indefinite. Specifically, the Examiner contends that the term "express at a very low level, β_3-AR" is not defined

clearly in the specification. Applicants respectfully disagree. The specification lists numerous examples of cells that express β_3-AR at low levels. For example, page 5 lines 11-13 of the specification states that β_3-AR is expressed by mouse brown adipose tissue cells, but is expressed at very low levels by human white adipocytes. See also, for example, page 29 lines 11-16 and page 51 lines 25-28 of the specification. The specification also points to two references (Wilson *et al.*, The Journal of Pharmacology and Experimental Therapeutics 279:214-221, 1996, cited on page 3 lines 19-20 of the specification and Strosberg, Annu. Rev. Pharmacol. Toxicol., 37:421-450, 1997, cited on page 51 lines 23-24 of the specification) that demonstrate low levels of β_3-AR expression. Thus, one skilled in the art could readily determine low levels of β_3-AR expression and could also readily identify cells that "express at a very low level, β_3-AR." Accordingly, Applicants believe this rejection has been overcome and respectfully request that this rejection be withdrawn.

REJECTIONS UNDER 35 USC § 102

The Examiner has rejected claims 28-29 and 31 as anticipated by Ito (Diabetes (1998) Vol. 47 p.1464-1471). The Examiner contends that Ito characterizes both human and mouse β_3-AR regulatory elements and that addition of the agonist CGP-12177, which resulted in an increase of oxygen consumption, constitutes contacting cells capable of producing β_3-AR trans-activating factor with

a test compound.

Claim 28 has been amended to recite "(a) contacting cells capable of producing the Sp1 or B segment-binding β_3-AR *trans*-activating factor and (b) detecting an increase in the level of activity of the Sp1 or B segment-binding β_3-AR *trans*-activating factor." Ito does not disclose either the Sp1 or B segment-binding β_3-adrenergic receptor *trans*-activating factors and thus does not anticipate claim 28 (or its dependent claim 31). Accordingly, Applicants respectfully request that this rejection be withdrawn.

Claim 29 recites that the increase in activity is detected by "an increase in the level of expression of *a reporter gene*..." (emphasis added). Ito does not disclose the use of a reporter gene to measure gene expression and therefore does not anticipate claim 29. Accordingly, Applicants respectfully request that this rejection be withdrawn.

REJECTIONS UNDER 35 USC § 103

The Examiner has rejected claims 28, 33 and 36 as obvious over Granneman (U.S. Pat. 5,364,772). The Examiner contends that it would have been obvious to construct vectors comprising the upstream elements for the human β_3-AR gene for use in their methods of screening for modulatory compounds.

As amended, claims 28 and 33 recite two β_3-AR *trans*-activating factors: Sp1 and segment B-binding β_3-AR *trans*-activating factors. Granneman

does not disclose or suggest these factors. In addition, Granneman does not detect or suggest detection of an increase in the level of activity of these factors. The segment B-binding β_3-AR *trans*-activating factor is novel and it was not known in the art that Sp1 factors were β_3-AR *trans*-activating factors. Thus, it would *not* have been obvious to one skilled in the art to screen for compounds that increase activity of either of these β_3-AR *trans*-activating factors. Thus, Applicants assert that neither claims 28 or 33 (or its dependent claim 36) are obvious. Accordingly, Applicants respectfully request the rejection be withdrawn.

ALLOWABLE CLAIMS

The Examiner has objected to claims 30 and 34 because they are dependent on rejected claims and has stated that they would be allowed if rewritten in independent form. Claim 34 has been amended to be in independent form and to incorporate the limitations of the claim upon which it depended (claim 33). Thus, the objection to claim 34 has been overcome and Applicants respectfully request that this objection be withdrawn and that claim 34 be allowed.

Claim 30 has been amended to depend upon claim 28. Claim 30 incorrectly recited that it was a method "according to claim 29;" it should have recited that it was dependent upon claim 28. Incorporating the limitations of claim 29 into claim 30 is incompatible with incorporating the limitations of claim 28 into claim 30; claim 29 requires detecting an increase in the level of expression of a

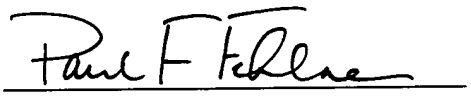
reporter gene, while claim 30 requires detecting an increase in the amount of β_3-AR *trans*-activating factor. Therefore, claim 30 has been amended to depend from claim 28. Applicants believe that the objection to claim 30 has been overcome and respectfully request that this objection be withdrawn and that claim 30 be allowed.

CONCLUSION

Therefore, in view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,



Paul F. Fehlner, Ph.D.
Reg. No. 35,135
Attorney for Applicants

DARBY & DARBY, P.C.
Post Office Box 5257
New York, NY 10150-5257
Phone (212) 527-7700

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Docket No: 0630/1E791-US1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Vedrana S. SUSULIC; Emir DUZIC

Serial No.: 09/761,116 Art Unit: 1636

Confirmation No.: 3094

Filed: January 16, 2001 Examiner: Leffers Jr., Gerald

For: TRANSCRIPTIONAL REGULATION OF THE HUMAN BETA3 - ADRENERGIC RECEPTOR GENE

MARK-UP AMENDMENT

Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

October 16, 2002

Sir:

28. (Amended) A method of screening for a compound that increases activity of [a] an Sp1 or B segment-binding β_3-adrenergic receptor (β_3-AR) *trans-*

activating factor in human cells, which method comprises:

(a) contacting cells capable of producing the Sp1 or B segment-binding β_3-AR *trans*-activating factor with a test compound; and

(b) detecting an increase in a level of activity of the Sp1 or B segment-binding β_3-AR *trans*-activating factor.

29. (Amended) A method [according to claim 28] of screening for a compound that increases activity of a β_3-adrenergic receptor (β_3-AR) *trans*-activating factor in human cells, which method comprises:

(a) contacting cells capable of producing the β_3-AR *trans*-activating factor with a test compound; and

(b) detecting an increase in a level of activity of the β_3-AR *trans*-activating factor, wherein the increase in the level of activity of the β_3-AR *trans*-activating factor is detected by detecting an increase in the level of expression of a reporter gene operatively associated with an isolated nucleic acid having a nucleotide sequence GCCTCTGGGGAG (SEQ ID NO:1) relative to a level of expression prior to contact with the test compound.

30. (Amended) A method according to claim [29] 28, wherein the increase in the level of activity of the β_3-AR *trans*-activating factor is detected by

detecting an increase in the amount of β_3-AR *trans*-activating factor present in the cells after contacting them with the test compound relative to the amount present prior to contact with the test compound.

33. (Amended) A method of screening for a compound that inhibits activity of [a] an Sp1 or B segment-binding β_3-adrenergic receptor (β_3-AR) *trans*-activating factor in human cells, which method comprises:

(a) contacting cells capable of producing the Sp1 or B segment-binding β_3-AR *trans*-activating factor with a test compound; and

(b) detecting a decrease in a level of activity of the Sp1 or B segment-binding β_3-AR *trans*-activating factor.

34. (Amended) A method [according to claim 33] of screening for a compound that inhibits activity of a β_3-adrenergic receptor (β_3-AR) *trans*-activating factor in human cells, which method comprises:

(a) contacting cells capable of producing the β_3-AR *trans*-activating factor with a test compound; and

(b) detecting a decrease in a level of activity of the β_3-AR *trans*-activating factor,

wherein the decrease in the level of activity of the β_3-AR *trans*-activating factor is

detected by detecting a decrease in the level of expression of a reporter gene operatively associated with an isolated nucleic acid having a nucleotide sequence GCCTCTGGGGAG (SEQ ID NO:1) relative to a level of expression prior to contact with the test compound.

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